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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/054,365	11/12/2001	Carol W. Readhead	18810-81606	9234

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EXAMINER
SINGH, ANOOP KUMAR

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/054,365	READHEAD ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *183-186, 189-196, 199-205 and 208-257* is/are pending in the application.

4a) Of the above claim(s) *212-257* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *183-186, 189-196, 199-205 and 208-211* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the claims and specification filed August 31, 2007 has been received and entered. Applicants have amended claims 183-186, 189-196, 199-205, 208-210 and 211, while claims 1-182, 187-188, 197-198, 206, 207 have been canceled. Applicants have also added claims 212-257 directed to a method of producing a transgenic nonhuman mammal progeny.

Election/Restrictions

Applicant's election of Group I drawn to non-human transgenic vertebrate was acknowledged. Claims 183-186, 189-196, 199-205, 208-210 and 211 are drawn to elected subject matter and currently under examination as they are drawn to a non-human transgenic vertebrate. It is noted that newly added claims 212-257 read on non elected subject matter of group III (claim 151) that was withdrawn and subsequently canceled after restriction requirement, hence, claims 212-257 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 1/9/2004.

Claims 183-186, 189-196, 199-205, 208-210 and 211 are under examination.

Maintained-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 183-186, 189-196, 199-205, 208-210 and 211 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants' arguments have been fully considered by are not fully persuasive. Applicants' argue that although examples are given only in the mouse, but it is generally agreed that most mammals have similar physiology and anatomy and so it is entirely credible and expected that exemplification in the mouse provides adequate guidance to the skilled person to realize the invention in other mammals (see page 20 of the argument). Applicants also assert that parent patent (6,313,692) has been found enabling for a method of incorporating polynucleotide into the germ cell of a nonhuman mammal (see page 22 para. 1 of the argument).

As an initial matter it is noted that claims are directed to a nonhuman mammal or its progeny whose genome comprises any xenogeneic polynucleotide encoding any gene product of any phenotype and not to an *in vivo* method of incorporating a polynucleotide into germ cell of a male non human mammal as argued by the applicants (emphasis added). Although method of incorporating a polynucleotide in the germ cells of nonhuman mammal as set forth in the instant specification may be enabling, however, claims are not directed to a method rather instant enablement rejection is applied for not describing in the specification how one skilled in the art would make use of the claimed products. In this context, it is noted that specification contemplated the novel genetic modification or characteristic may be encoded by one or more genes, or may be caused by removal or mutation of one or more genes. The specification also contemplated a gene's function may be expressed to inactivate one of a pair of genes (alleles), or inactivation of genetic material by mutation or deletion of gene sequences, or by

expression of a dominant negative gene product or artificially induced mutations or variations (see para. 29-29 of the specification). The specification also contemplated expression of a previously unexpressed trait, augmentation or reduction of an expressed trait, over expression or under expression of a trait, ectopic expression (see para. 31 of the specification). The specification has exemplified a method to make transgenic mouse comprising GFP. However, the issue is not whether a correlation of mouse to other nonhuman mammal could be made as argued by the applicants instead issue is whether claimed nonhuman mammal has any enabled use that could be extrapolated to the breadth of the claim. In fact, analysis is based on a transgenic nonhuman mammal comprising in its genome a xenogeneic polynucleotide encoding any gene product that may include mutation or deletion of gene sequences, or by expression of a dominant negative gene product or any other genus of gene product. Examiner has cited a number of references to demonstrated that one skilled in art would not know how to use the claimed product particularly in view of unpredictability in achieving a specific phenotype or level of expression in plurality of different mammal. It is generally known that only mouse is routinely manipulated animal and prior art recognized the unpredictability of obtaining transgenic animals with a specific phenotype as summarized by the references of Kappell et al, Mullins et al, Ebert and Holschneider. Earlier, Hammer et al. (Journal of animal Science, 986, 63, 269-278) reported that the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. Ebert et al (Mol Endocrinol. 1988; 2(3): 277-83) reported a transgenic pig that did not develop an expected phenotype of growth during the rapid growth phase, when transfected with a Moloney murine leukemia virus rat somatotropin fusion gene (p. 277, summarized in abstract). Thus, at the time of filing, the resulting phenotype of a transgenic nonhuman

mammal was considered unpredictable and multiple compensatory pathways confounded it. An Artisan of skill would need to perform further research upon the nonhuman mammal obtained by the process disclosed in the instant application in order to determine the correlation between the transgene and the observed phenotypes or effect. In absence of any specific teaching an artisan of skill would have to perform undue experimentation to make use of the invention. An artisan would have to perform undue experimentation to determine the appropriate elements that would specifically express genus of different genes in any nonhuman mammal showing expected phenotype. Absent of evidence to the contrary, it is not clear that resulting phenotype of a nonhuman mammal comprising genus of gene product of known or unknown biological function in presence of any promoter would result in any specific phenotype particularly in view of unpredictably expressed in transgenic art. An artisan would not know how to use resulting transgenic nonhuman mammal made by the method described in the specification and therefore would require undue experimentation to determine how to use the resulting transgenic nonhuman mammal.

Applicants' argue that many technologies are readily and widely applied to different mammalian species, once established in the mouse, without undue burden. For example: *in vitro* fertilization mice, rats, pigs, monkeys, humans); cloning (mice, sheep, pigs, monkeys); magnetic resonance imaging (MRI) (mice, rats, monkeys, humans), as well as numerous biochemical assays such as hormone levels, red blood cell levels, blood and urinary 'biochemical tests. Applicants assert that examiner has provided no evidence that the teachings of the patent application cannot be used in other mammalian species, and for all the reasons given above.

In response, examiner has already provided evidence that the one skilled in the art would not know how to use the resulting transgenic nonhuman mammal particularly since instant claims embrace potentially any genetic modification in the genome of the nonhuman mammal (see preceding section). Given the

unpredictability in obtaining transgenic nonhuman mammal with specific phenotype, one skilled in the art would have to make new invention in the field to make transgenic nonhuman mammal comprising polynucleotide encoding a specific gene product and then characterize the phenotype of said transgenic animal to determine the correlation between the transgene and the observed phenotypes or effect. An artisan would have to perform undue experimentation to determine the appropriate elements that would specifically express genus of different genes in any nonhuman mammal showing expected phenotype without resonable expectation of success for the reasons discussed in previous office action dated 3/1/2007.

With respect to applicant's argument that althogh some isolated cases transgenes that have been integrated into the genome, had unexpected expression patterns, the vast majority of transgenes are expressed in a predictable way, it is emphasized that applicants' arguments are not commensurate in scope with the breadth of the claims. Specifically claims are directed to a transgenic nonhuman mammal comprising in its genome a polynucleotide encoding a gene product that may be expressed to inactivate one of a pair of genes (alleles), or inactivation of genetic material by mutation or deletion of gene sequences, or by expression of a dominant negative gene product or artificially induced mutations or variations (see para. 29-29 of the specification). Thus, the claimed invention not only encompasses random integration of the transgene, but specific integration of the transgene in a specific, genomic target. Examiner has provided adequate evidence to show that numerous factors that contribute to the resulting phenotype of transgenic nonhuman mammal, including compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the inactivated gene. It is also known in prior art that a given construct may react very differently from one species to another (see office action dated 3/1/07).

Applicants also argue that instant specification has confirmed that transgenic mouse progeny can be generated from male mice that have transduced sperm by infection of the male germ cells *in vivo* and subsequent natural mating (see page 21 bridging page 22 of the argument section).

In response, it is noted that Examiner would agree that instant specification teaches a method of producing transgenic mouse progeny from male mice that have transduced sperm by infection of the male germ cells *in vivo* and subsequent natural mating. However, the issue is not whether transgenic mouse progeny could be obtained, rather in the instant case, claims embrace any nonhuman transgenic mammal comprising a lentiviral vector comprising at last one xenogenic polynucleotide encoding any gene product. It is emphasized that claim 183-184, 189, 190-191, 197 are drawn to nonhuman transgenic mammal generated by administering a lentiviral vector comprising at least one polynucleotide into the testis. The specification has exemplified administering genetic material (GFP) into the testis of a mouse and reverse transcriptase PCR (RTPCR) analysis of tissues obtained from the testis showed presence of GFP in the injected testes, but not in the control testes. It is noted that specification only teaches administration of lentiviral vector directly into testis resulting in expression of gene in the testis. It is emphasized that neither prior art nor instant specification teaches that a F0 founder animal would show presence of polynucleotide in most of the other cells as required by transgenic nonhuman mammal produced by direct injection of the vector into the testis of the male mammal. In other words, nonhuman mammal produced by the method set forth in claim 183-184, 189, 190-191, 197 would be founder animal and not transgenic as required by the claim.

Withdrawn-Claim Rejections - 35 USC § 112

Claims 183-186, 189-196, 199-205, 208-210 and 211 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point

out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

Withdrawn-Claim Rejections - 35 USC § 102

Claims 183-184, 187, 189, 190-194, 197, 199-203, 206-211 rejected under 35 U.S.C. 102(b) as being anticipated by Jordan et al (Journal of Virology, 1995, 69 (11), 7328–7333) is withdrawn in view of amendments to the claims.

Claims 183-186, 189-196, 199-205, 208-210 and 211 rejected under 35 U.S.C. 102(b) as being anticipated by Jolicoeur et al (Us Patent 5574206 dated 11/12/1996) is withdrawn in view of amendments to the claims.

New -Claim Rejections- Necessitated by amendments- 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 183-186, 189-196, 199-205, 208-210 and 211 remain rejected under 35 U.S.C. 102(e) as being anticipated by Bryant et al (US Patent 6156952 dated 12/5/2000, effective filing date 4/19/1998).

Instant claims are product by process claims.

It is noted that applicants' have amended claims to require xenogeneic polynucleotide that is xenogeneic to both vector and mammal, a limitation that was

not required by earlier presented claims. Therefore, instant rejection is proper with respect to addressing new limitation of the claim. In addition, it is noted that instant application claims priority from US provisional application no. 60/065,825, dated 11/14/1997, however, upon review examiner could not find support for a nonhuman mammal whose genome comprises lentiviral vector in application no. '825. Thus, effective filing date of instant application is 11/13/1998.

Bryant et al teach transgenic non-human animal whose genome comprises lentiviral (e.g., HIV) and at least one additional transgene including human CD4 receptor gene or a gene involved in a disease (see col. 13, lines 15-50). In addition, Bryant et al also disclose a method of producing the transgenic nonhuman animal described identification and quantitation of transgenes in the founder animals and their progeny (see col. 14 and 15). Bryna et al contemplate transgenic animal of the invention includes mouse, rat, rabbit, pigs, baboons and monkeys (see col. 10, lines 48-52). Thus, transgenic nonhuman animal and their progeny carrying a lentiviral and a gene involved in disease, wherein both vector and transgene is xenogeneic to the host mammal would meet the structural limitation of instant claims. Since the nonhuman animal and its progeny disclosed by Bryant is transgenic, hence, nonhuman mammal would contain the virus and transgene in the germ cell as well as somatic cell. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at

433. Thus, products disclosed by Bryant anticipates instantly claimed product. Furthermore, MPEP § 2113 states, "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Accordingly, Bryant et al anticipates claims 183-186, 189-196, 199-205, 208-210 and 211.

Claims 183-186, 189-190, 196, 199-200, 203-205, 208-210 and 211 remain rejected under 35 U.S.C. 102(b) as being anticipated by Leonard et al (AIDS Res Hum Retroviruses. 1989; 5(4): 421-30).

Instant claims are product by process claims.

It is noted that applicants' have amended claims to require xenogeneic polynucleotide that is xenogeneic to vector and mammal, a limitation that was not required by earlier presented claims. Therefore, instant rejection is proper with respect to addressing new limitation of the claim.

Leonard et al teach transgenic mice containing the HIV LTR linked to the bacterial gene encoding chloramphenicol acetyltransferase (CAT) (see abstract). In addition, Leonard et al also disclose founder transgenic mice mated with syngeneic non-transgenic mouse to obtain transgenic mouse (see page 423, last para.). Thus, transgenic mouse and its progeny carrying a lentiviral comprising a CAT gene, wherein both vector and transgene is xenogeneic to the host mammal would meet the structural limitation of instant claims. Since the transgenic mice and its progeny disclosed by Leonard are transgenic, hence, transgenic mouse disclosed by Leonard would contain the virus and transgene in the germ cell as well as somatic

cell. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433. Thus, products disclosed by Bryant anticipates instantly claimed product. Furthermore, MPEP § 2113 states, "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Accordingly, Bryant et al anticipates claims 183-186, 189-190, 196, 199-200, 203-205, 208-210 and 211.

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Jolicoeur et al (Us Patent 5574206 dated 11/12/1996).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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